Chapter 1
The Importance of Molecular Chaperones in Survival and Pathogenesis of the Malaria Parasite *Plasmodium falciparum*

Jude Przyborski

It has been estimated that one child dies of malaria every minute. Although massive research efforts have been directed towards the fight against this deadly disease, still over 0.6 million people fall victim to malaria every year, and approximately half of the world's population live in malaria risk areas (World Health Organization 2011). Malaria impacts not just the fate of individuals, but also the countries in which they live. Countries with high rates of malaria have an annual growth rate lower than those which are free of, or have eradicated the disease (Gallup and Sachs 2001). Thus, malaria in the modern world is part of a vicious circle of poverty and disease, with those most at need of help concomitantly being those least economically able to help themselves. In addition to the socioeconomic challenges involved in reduction of malaria occurrence across the world, the parasite itself is fighting back.

Chloroquine, once seen as the "magic bullet" against malaria first became ineffective in the 1950s due to rapidly spreading resistance in the parasite population. Indeed the parasite has become resistant to all but the latest artemisinins, dramatically limiting the options available to clinicians (White 2004). Although several experimental malaria vaccines are currently under trial, so far none has shown the potential to be used successfully on a global scale (Vaughan and Kappe 2012).

While improvements in the prevention and management of malaria will always be on the global agenda, new therapeutic targets are also desperately needed for the treatment of malaria. To this end, a concerted research effort has been directed towards understanding the basic biology of malaria parasites, with a view to identifying targets and strategies with potential to roll back the burden of malaria on individuals and communities.

This book concentrates on our current knowledge on the role of heat shock proteins in the survival of malaria parasites, and their interaction with the host. Malaria parasites, in common with most other organisms, possess a large complement of proteins designed to protect the cell against changing environmental and intracellular

J. Przyborski (✉)
FB Biology, Philipps University Marburg,
35043 Marburg, Germany
e-mail: Przybors@staff.uni-marburg.de

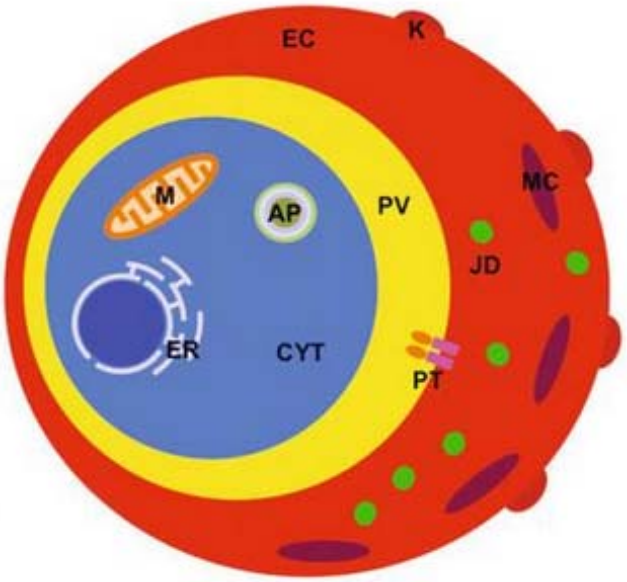

Fig. 1.1 Localisation and function of heat shock proteins in the malaria-infected cell. Parasite, *blue*; parasitophorous vacuole (*PV*), *yellow*; erythrocyte, *red*. Heat shock proteins have been shown, or are predicted, to play a role in processes taking place in the parasite cytosol (*CYT*), endoplasmic reticulum (*ER*), apicoplast (*AP*), mitochondria (*M*), parasitophorous vacuole (*PV*), in association with the PTEX complex (*PT*), within the cytosol of the erythrocyte (*EC*), associated with knobs (*K*), J-dots (*JD*) and Maurer's clefts

conditions. Many of these proteins belong to the class of heat shock proteins. Since their initial discovery in *Drosophila*, many different members of this family have been identified and characterized in detail. Although originally implicated in cellular protection against thermal insult, we now know that members of the heat shock class of proteins are involved in numerous and varied cellular processes including folding of nascent proteins, protein quality control and degradation, protein trafficking and protein refolding following cellular stress. Due to their involvement in helping proteins fold (or re-fold) into their correct three dimensional structures, some members of the Hsp class are also referred to as molecular chaperones.

Parasites, by definition, survive and multiply within a host organism or cell. Although the parasitic way of life comes with benefits such as a ready supply of sufficient nutrients, it also entails the parasite giving up a certain level of independence. Thus, parasites must endure whichever conditions their host experiences, but over which they have no direct influence. Additionally, many parasites require passage through several different hosts and possibly "free-living" or egg stages to complete their life-cycle, further increasing the stresses endured. To enable the parasite to survive such changing and unpredictable times, it has been noted that, against a background of general genomic reduction, many parasites still contain a large complement of heat shock proteins. This fact suggests that many parasites depend heavily on heat shock proteins to survive, making them a potentially attractive drug target.

Recent studies have revealed that *Plasmodium* encodes a wide variety of heat shock proteins, which are involved in many essential and novel cellular processes. Within the parasite itself, heat shock proteins have been found in both the cytosol, apicoplast, ER and mitochondria (Fig. 1.1). These proteins generally carry out housekeeping functions or are involved in protein trafficking, akin to processes found in other systems. Upon invading the host erythrocyte, the parasite massively modifies

its host cell. This "cellular renovation" is thought to be mediated by parasite-encoded proteins which are transported from the parasite to the host cell. Trafficking of these proteins to their respective cellular localisation involves the action of a wide range of heat shock proteins, themselves with diverse localisation (Fig. 1.1). In the following chapters world experts in malaria heat shock proteins give a detailed overview of our current state of knowledge, detailing their role in both typical, but also atypical processes within the infected cell. These articles highlight that the malaria parasite, as in so many things, obeys the adage "The same. But different".

References

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